Risk Characterization of Subchronic Inhalation Exposure to Methyl Bromide

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Risk Assessment Basics

How toxic is methyl bromide?

What is the human exposure level?

$$MOE = \frac{NOEL}{Exposure}$$

MOE = Margin of exposure
NOEL = No-observed-effect level
LOEL = Lowest-observed-effect level
ENOEL = Estimated NOEL, LOEL/UF

Risk Assessment Basics

- Reference concentration
  - Account for species breathing rate differences
- Critical NOEL - Weight of evidence
  - Quality of study
  - Relevance of endpoint
  - Comparison of NOELs/LOELs
  - Time and dose relationship

Risk Assessment: Inhalation Exposure

- 1992 Preliminary Risk Assessment
- 1999 Draft Risk Characterization Document
- 2002 Final Risk Characterization Document
- 2003 Addendum to the Final RCD

RCD=Risk Characterization Document

Risk Assessment: Inhalation Exposure

- 1992 Preliminary Risk Assessment
  - Acute exposure
  - Structural fumigation

Risk Assessment: Inhalation Exposure

- 1999 Draft Risk Characterization Document
  - Acute, short-term, subchronic, and chronic exposures
  - Structural, commodity, and field fumigations
  - U.S. EPA and OEHHA reviews
  - National Research Council (NRC) review

1999 RCD - NRC Review

- Endpoints and NOELs - appropriate
- Toxicity endpoint - conservative
- Exposures - underestimated
- Recommendations:
  - Additional toxicology studies
  - Additional monitoring studies

1999 RCD - Subchronic Inhalation Toxicity

- DPR
  - ENOEL = 0.5 ppm (Newton study), UF=10
  - Dog as most sensitive species
  - Effect consistent with neurotoxicity, severe effects at higher doses
- NRC
  - NOEL was reasonable, based on neurotoxicity
  - However,
    - Effect was equivocal
    - Experimental design concerns: number of dogs, protocol used
  - Recommended a new study

2002 RCD - Subchronic Inhalation Toxicity

- Final RCD for inhalation exposure
  - Toxicology: no new studies
  - Exposure: revised exposures
  - Risk characterization
    - MOE based on ENOEL of 0.5 ppm (Newton Study)
    - LOEL of 5 ppm and uncertainty factor of 10
  - Conclusion
    - MOEs for most subchronic exposures < 100

New Subchronic Inhalation Toxicity Study - Registrant

- Design (Schaefer, 2002)
  - Dogs were exposed at 0, 5, 10, or 20 ppm for 6 weeks
  - 4/sex/group
  - Evaluated using tests specific for neurotoxicity
- Author's conclusion
  - No effects observed at any dose
  - NOEL = 20 ppm
- Registrant external review (Dr. J. Chambers)
  - NOEL = 20 ppm
  - Use study for risk assessment

New Subchronic Inhalation Toxicity Study - Reviews

- Medical Toxicology Branch review
  - NOEL is 5 ppm (majority) or < 5
  - Lack of proprioceptive placing at 10 ppm and 20 ppm
  - Tremors and twitching in one dog at 5 ppm - due to illness?
- Expert external review - Dr. K. Pinkerton (UC Davis, School of Veterinary Medicine)
  - New study appropriate for safety standards
  - Lack of proprioceptive placing was treatment-related
  - NOEL = 5 or 10 ppm

Subchronic Inhalation Exposure Risk Characterization

- DPR proposed revision of critical NOEL
  - Weight of evidence
    - Studies in rats and dogs showed NOELs around 5 ppm (Table 1)
    - Dogs are more sensitive to methyl bromide
  - Critical estimated NOEL of 1.7 ppm
    - Based on a LOEL of 5 ppm in Newton study
    - Uncertainty factor of 3 instead of 10
    - Lower NOEL than Schaefer study (5 ppm) but greater uncertainty

Table 1. No-Observed-Effect Levels and endpoints for methyl bromide subchronic toxicity.

Studies	Effect	NOEL	Reference concentrations	
			Adult	Child
Newton, 1994a Dog	Unresponsiveness	*<5 ppm (ENEL 0.5 ppm)* *UF=10*	*2 ppb*	*1 ppb*
		< 5 ppm (ENEL 1.7 ppm) UF=3	5 ppb	3 ppb
Schaefer, 2002 Dog	Tremors, twitching, emesis	<5 ppm UF=3	5 ppb	3 ppb
	Absence of Proprioceptive placing response	5 ppm	16 ppb	9 ppb
	No Effects	20 ppm	63 ppb	36 ppb
Norris *et al.*, 1993 a and b Rat	Brain weight reduction	<30 ppm UF=10	20 ppb	11 ppb

Subchronic Inhalation Exposure Risk Characterization

- Expert external review - Dr. J. Last (UC Davis, Toxic Substances Research and Teaching Program)
  - Review of Schaefer study and database
  - Recommendations
    - Schaefer study was scientifically sound
    - Effects are expected to be equivocal near the NOEL
    - NOEL = 5 ppm for risk assessment

Subchronic Inhalation Exposure Risk Characterization

- DPR Addendum to 2002 RCD for inhalation
  - No new exposure data
  - Critical subchronic NOEL = 5 ppm instead of 0.5 ppm
    - Recommendations from internal and external expert reviews
    - Greater certainty with experimental NOEL
    - Comparison of reference concentrations

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Table 2. Critical No-Observed-Effect Levels and endpoints for methyl bromide risk characterization.

Scenarios	Experimental NOEL	Reference Concentration[d]	Effects in Animal Studies
Acute	40 ppm	210 ppb	Developmental toxicity (pregnant rabbit)
Subchronic 1 week 6 weeks	20 ppm 5 ppm	120 ppb(adult) 70 ppb (child) 16 ppb (adult) 9 ppb (child)	Neurotoxicity (pregnant rabbit) Neurotoxicity (dog; Schaefer, 2002)
Chronic	0.3 ppm (ENEL)	2 ppb (adult) 1 ppb (child)	Nasal epithelial hyperplasia/ degeneration (rat)

Subchronic Inhalation Exposure Risk Characterization

	Schaefer study NOEL	Effects in Schaefer study	Study to set regulatory level
Registrant	20 ppm	None, need other supportive or histological evidence	Schaefer, 2002
Pinkerton*	5 or 10 ppm	Lack of PPR is tx-related, histological support not needed	Schaefer, 2002
Last	5 ppm	Lack of PPR is tx-related, equivocalness expected near NOEL	Schaefer, 2002 and database showed 5 ppm
DPR	5 ppm	Lack of PPR is tx-related	Schaefer, 2002 and database

PPR=proprioceptive placing response, **tx**=treatment
* Dr. Pinkerton reviewed only the Schaefer study.